AS ABSTRACT

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TI 5-Hydroxytryptamine and other indole derivatives
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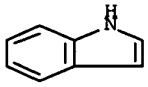
DT Patent
LA Unavailable
FAN.CNT 1
PI ES----227606 19570301 ES <--
AB A new synthesis of 5-hydroxytryptamine (I) and similar compds. was described as well as the isolation of intermediates. A mixture of 100 g. p-benzyloxyaniline, 120 ml. $H_2O$, and 76 ml. concentrated HCl was diazotized at 0° by a solution of 32.5 g. $NaNO_2$ in 100 ml. $H_2O$. Then 120 g. AcONa was added and the cold (0°), stirred solution was added dropwise to 66.5 g. α-carbethoxycyclopentanone. After 3 hrs. of stirring at 20° the mixture was filtered, the precipitate washed wtith $H_2O$, mixed with 1200 ml. 5% NaOH solution and kept 3 hrs. on a steam bath. The pH of the hot solution was adjusted to 7.5 (HCl), activated C was added, and the solution filtered. The cold filtrate was acidified (HCl), 128 g. crystalline p-benzyloxyphenylhydrazone of α-oxoadipic acid (II) was filtered out and recrystd., m. 148-9° (50% EtOH). A mixture of 125 g. II with 1250 ml. anhydrous dioxane containing 5% dry HCl was refluxed 20 min., cooled, the precipitated $NH_4Cl$ was filtered out and washed with dioxane, the filtrate mixed with enough 10% solution of $Na_2CO_3$ to bring the pH to 8. Dioxane was removed at 20 mm., the 300-400 ml. residue was neutralized to pH 7.2, filtered with active C and acidified with HCl to Congo red. 5-Benzyloxy-2-carboxy-3-indolepropionic acid (III) (103 g.) was isolated by filtering, washing (neutral litmus) and drying on a steam bath; recrystd. from 50% EtOH, III m. 188-90°. Further recrystns. gave m.p. 191-2°. A mixture of 80 g. III and 800 ml. paraffin oil was heated 90 min. to 210°, cooled to 60°, extracted with 300 ml. 10% $Na_2CO_3$ solution, neutralized to pH 7.2 and filtered with active C. The filtrate was acidified (dilute HCl) and 5-benzyloxy-3-indolepropionic acid (IV) precipitated (62 g., m. 150-1°). Recrystn. (50% EtOH) gave 48 g. of IV. Further recrystn. gave m.p. 163-5°. For the Me ester of IV (V), a solution of 42 g. IV in 420 ml. abs MeOH containing 3% of dry HCl was refluxed 2 hrs., then cooled and poured into a solution of 43 g. $NaHCO_3$ in 900 ml. $H_2O$. Crystalline V was filtered out, washed ($H_2O$) and dried (43.3 g., m. 98-9°). Recrystd. from MeOH m. 100-1°. A hydrazide of IV (VI) was obtained when a solution of 43 g. V and 63 ml. hydrazine in 1160 ml. EtOH was refluxed 1 hr., most of the solvent was removed at reduced pressure and $H_2O$ was added to precipitate 40.8 g. crystalline VI. This recrystd. (70% EtOH and then $H_2O$) m. 137-8°. The azide of IV (VII) was obtained when a solution of 40 g. VI in 120 ml. HOAc was stirred, mixed with 510 ml. $H_2O$ and 300 ml. $C_6H_6$ then cooled to 0°. A 10% solution of $NaNO_2$ in 100 ml. $H_2O$ was added within 5 min. The $H_2O$ layer was twice extracted with 330-ml. portions $C_6H_6$. The combined $C_6H_6$ solns. (at 0°) were washed with a dilute $NaHCO_3$ solution, then with cold $H_2O$ to neutral reaction and dried over anhydrous $Na_2SO_4$. A small part of the $C_6H_6$ solution was freed of the solvent to give crystalline, crude VII (decompose at 45°). Me β-[3-(5-Benzyloxy)indolyl]ethyl carbamate (VIII) was obtained when the remainder of the $C_6H_6$ solution of VII was added dropwise to 3300 ml. boiling anhydrous MeOH, the $C_6H_6$-MeOH azeotrope was distilled, the MeOH solution was refluxed 1 hr. and the MeOH removed under reduced pressure. The residue diluted with $C_6H_6$ was passed through a column with 70 g. $Al_2O_3$ and eluted with $C_6H_6$. The volume was reduced in vacuo to 150 ml. and 15 ml. hexane was added; 27 g. crystalline VIII, m. 90-3°, was obtained. The mother liquor yielded further 4.5 g. of VIII. VIII recrystd. twice from $C_6H_6$ m. 94-5°. Hydrogenation of VIII in MeOH, at 5 atmospheric and 25° by H in the presence of palladized C gave Me β-[3-(5-hydroxy)indolyl]ethylcarbamate (IX). The MeOH solution of IX was refluxed 30 min. with 150 ml. 1:1 HCl to hydrolyze the ester. The resulting green solution was mixed with 9 g. NaOAc, neutralized to Congo red with $NaHCO_3$, and filtered. The filtrate was mixed with 20.8 g. picric acid, the MeOH was removed in vacuo, the residue diluted to 400 ml. with $H_2O$ and filtered at 50-65° with activated C. From the cold filtrate crystallized a picrate of I; recrystd. from $H_2O$ m. 196-7°. II (128 g.), esterified by an excess of diazomethane gave 135 g. of di-Me ester of II (X), m. 114-15°. A mixture of 134 g. X with a 10% solution of dry HCl in 1660 ml. absolute MeOH was refluxed for 20

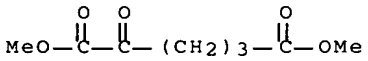
min., cooled, poured into a cold solution of 400 g. $NaHCO_3$ in 6000 ml. $H_2O$, the solid was filtered out and crystallized from EtOH; 96.5 g., crystalline 5-benzyloxy-2-methylcarboxy-3- indolepropionic acid Me ester (XI), m. 120-1°, was obtained. Further 16.5 g. of XI was recovered from the filtrate. XI twice recrystd. from EtOH m. 122-3°. A solution of 112 g. XI in 2250 ml. EtOH was mixed at 40° with 98.5° NaOH and 164 ml. $H_2O$, kept at 25° for 12 hrs., cooled to 0°, filtered and the precipitate was dissolved in a small amount of $H_2O$, decolorized by active C and precipitated by dilute HCl; 95 g. of III was obtained. Another method of transforming VIII into I was developed. IX (37 g.) in 520 ml. EtOH was kept overnight at 40-50° with 220 ml. 6N HCl; then 97.5 g. $NaHCO_3$ was added, the solid NaCl was filtered off and the filtrate mixed with 18.5 g. sodium salicylate was freed of most of the solvent in vacuo. The remaining 250 ml. was cooled and 18.5 g., crystalline salicylate of 5-benzyloxytryptamine, m. 167-9°, was separated A sample of the salicylate (XII) recrystd. formed white crystals, m. 174-5° ($H_2O$). XII was in the same way as VIII to give the salicylate of I which after treatment with picric acid gave a picrate of I (XIII). I was isolated via its oxalate (XIV). A stirred mixture of 5 g. XIII and 25 ml. N HCl was extracted with $Et_2O$ to remove all picric acid. The ethereal solution was extracted with 10 ml. N HCl and the aqueous layers were combined, neutralized (Congo red) to pH 7.8-7.9 with $NaHCO_3$ and extracted several times by BuOH. The combined exts. were washed with a NaCl solution (pH 7.9 adjusted by addition of $K_2CO_3$), dried ($Na_2SO_4$) and mixed with 3 g. oxalic acid in 25 ml. EtOH. The solvents were removed in vacuo; the residue dissolved in absolute EtOH, the warm solution was filtered with active C, cooled, mixed with anhydrous $Et_2O$ and the crystalline XIV was separated Recrystn. from EtOH-$Et_2O$ gave crystals, m. 195-7°. The ratio of I to oxalic acid in XIV was 1:1. A compound containing oxalic acid-I = 2:1 was made by using a double amount of oxalic acid. This dioxalate of I m. 193-5°. Di-Et ester of III (XV) was obtained when a suspension of 125 g. II in 500 ml. anhydrous $Et_2O$ was mixed with an excess of a solution of diazoethane in $CH_2Cl_2$; after 24 hrs. it was decomposed with dilute HCl and the $CH_2Cl_2$ removed. The crude XV was mixed with 3 l. $C_6H_6$; 1 l. was distilled to remove $H_2O$ and dry HCl was bubbled 1 hr. through the residue. The cold mixture was treated with a 5% solution of $NaHCO_3$, the $C_6H_6$ layer was separated, concentrated to 300 ml., mixed with 2500 g. $Al_2O_3$, eluted with 1:1 hexane-$C_6H_6$ and crystallized from EtOH. This gave XV, m. 108-9°. XV was also prepared by the reaction of II with absolute EtOH and dry HCl. When absolute MeOH was used instead of EtOH, XI was obtained. Iso-Am ester of III was obtained analogously using iso-AmOH. Benzoate of 5-benzyloxytryptamine (XVI) was obtained when 20 g. VIII was hydrolyzed similarly as IX but instead of the picric acid, 9 g. BzONa was added, the solvent was removed and the yellow precipitate of XVI, m. 148-9°, was separated Two recrystns. gave XVI, m. 153-4° ($H_2O$). XVI was to the benzoate of I (XVII) similarly as VIII; XVII was converted to XIII by treating it with picric acid. Alternate methods for preparation of I were developed. An ethereal solution of VII treated with EtOH gave Et[β-[3-(5-benzyloxy)indolyl]ethylcarbamat e (XVIII), m. 87-8°. XVIII was (in the same manner as VIII) to the 5-hydroxy derivative which was saponified and treated with picric acid to give XIII. A $H_2O$ solution of 10 g. I.HCl neutralized to Congo red was mixed with 2.7 g. creatinine, 420 ml. EtOH and 23.5 ml. 2N $H_2SO_4$. The mixture was heated and then cooled; white, crystalline double sulfate of 5-hydroxytryptamine creatinine was isolated and recrystd., m. 213-14° ($H_2O$). Iso-Am ester of IV (XIX) was prepared esterifying 72 g. IV with 720 ml. iso-AmOH containing 3% HCl. The solution of XIX was refluxed 1 hr. with 100 ml. hydrazine, cooled, washed repeatedly with $H_2O$ and very dilute HCl and then mixed with 180 ml. $H_2O$ containing 18 g. $NaNO_2$. To the cold (0°) mixture was added slowly 22.2 ml. concentrated HCl with 50 ml. $H_2O$. After 5 min. the alc. layer was separated and the $H_2O$ layer extracted with 300 ml. iso-AmOH. The combined alc. solns. were neutralized with cold, aqueous $NaHCO_3$, washed with cold $H_2O$ and dried over anhydrous $K_2CO_3$. The solution was then refluxed with $P_2O_5$ for 1 hr. A sample was freed of the solvent, dissolved in $C_6H_6$, chromatographed over $Al_2O_3$ and separated as yellow, glossy β-[3-(5-benzyloxy)indolyl]ethylcarbamate isoamyl ester (XX). The solution of XX was hydrogenated (see VIII) to give the corresponding hydroxy compound (XXI) which was hydrolyzed and I was isolated as XIII. The following alternative reaction procedures were described. The decarboxylation (III to IV) was performed in boiling tetrahydronaphthalene or decahydronaphthalene. Et ester of IV was made analogously to V using anhydrous EtOH. $PhCH_2$ ester analog of XX, m. 72-3°, was made as

described for XX using PhCH2OH instead of MeOH, the solution was hydrogenated (see VIII), and XIII was precipitated directly by addition of picric acid.

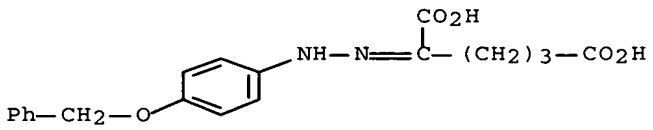
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Indole (9CI)
MF C8 H7 N
CI COM, RPS



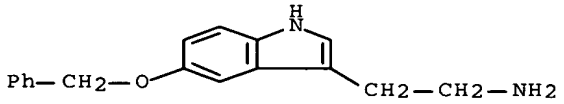
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Hexanedioic acid, 2-oxo-, dimethyl ester (9CI)
MF C8 H12 O5



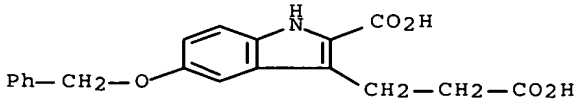
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Hexanedioic acid, 2-oxo-, [p-(benzyloxy)phenyl]hydrazone (6CI)
MF C19 H20 N2 O5



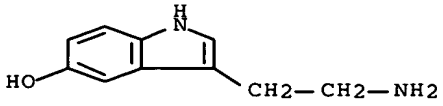
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Indole-3-ethanamine, 5-(phenylmethoxy)- (9CI)
MF C17 H18 N2 O
CI COM



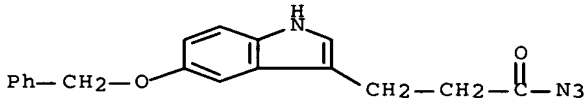
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Indole-3-propanoic acid, 2-carboxy-5-(phenylmethoxy)- (9CI)
MF C19 H17 N O5



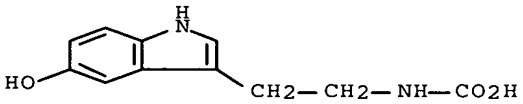
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI)
MF C10 H12 N2 O
CI COM



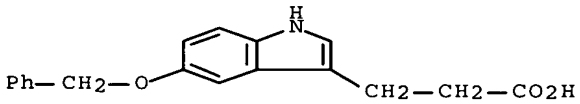
L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Indole-3-propionyl azide, 5-(benzyloxy)- (6CI)
MF C18 H16 N4 O2



L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Carbamic acid, [2-(5-hydroxy-1H-indol-3-yl)ethyl]- (9CI)
MF C11 H12 N2 O3
CI COM



L4 9 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Indole-3-propanoic acid, 5-(phenylmethoxy)- (9CI)
MF C18 H17 N O3



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